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Organochlorine Exposures and Breast Cancer Risk in New York City Women[1]

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A hospital-based case-control study of breast cancer risk related to organochlorine (OC) exposure was conducted in a multiethnic setting in New York City. We enrolled 175 breast cancer patients and 355 control patients. The overall racial/ethnic distribution was 57% Caucasian, 21% Hispanic, 22% African-American; cases and controls were frequency-matched by age and race/ethnicity. Tumor markers (estrogen and progesterone receptors, p53, erbB-2) were assessed and organochlorines (DDE, DDT, *trans*-nonachlor, and higher (HPCB) and lower (LPCB) chlorinated biphenyls) were measured in blood serum. Tumors among minority women were of slightly higher stage than among Caucasians, but tumor markers were similar across the racial/ethnic groups. DDE levels were highest among African-American and Hispanic women; DDT was highest among Hispanics; HPCBs were highest among African-Americans; LPCBs were lowest among Hispanics; and *trans*-nonachlor was highest among African-Americans. However, OC levels were not associated with risk for breast cancer, nor did OCs differ with respect to tumor stage or tumor markers. Higher DDE levels were associated with increasing body mass index (BMI), but with decreasing level of education, frequency of nulliparity, and frequency of family history of breast cancer. HPCB levels decreased with BMI and were not correlated with breast cancer risk factors. These relationships can be attributed to historical patterns of exposure and to metabolic differences in OCs related to BMI.

Key Words: **breast cancer; DDT; PCB; ethnic; BMI; *trans*-nonachlor.**

INTRODUCTION

Wide variations exist in breast cancer risk among different racial, ethnic, geographic, and migrant groups. Environmental factors, including diet and lifestyle, have been widely investigated, but these variables have not been able to explain international or ethnic variability in the disease. In the United States, Hispanic-American women have a lower incidence of breast cancer than Caucasians, approximately 70 per 100,000 women (Anon, 1996) or less in different locales compared to Caucasians, whose rates are over 100 per 100,000 (Wolfgang *et al.*, 1991; Eidson *et al.*, 1994). Lower rates in certain racial/ethnic groups have been attributed to differences in reproductive factors; examples are Hispanic and Asian women, who experience earlier childbirth, higher parity, and longer lactation (Gray *et al.*, 1980). However, these and other known risks do not explain the wide disparities in breast cancer among racial/ethnic groups. African-American and Caucasian women have similar breast cancer incidence (95–115 cases per 100,000 women; Miller *et al.*, 1996), but breast cancer among African-American women occurs at younger ages. Breast cancer among African-American women has a poorer prognosis regardless of age at diagnosis; this has been associate with more advanced stage of disease at diagnosis, as well as other factors (Eley *et al.*, 1994).

Environmental exposures including DDT[2] and polycyclic aromatic hydrocarbons have received much attention as potential etiologic agents in breast cancer (Mussalo-Rauhamaa *et al.*, 1990; Hel-

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[2]Abbreviations used: HPCB, higher chlorinated polychlorinated biphenyls; LPCB, lower chlorinated polychlorinated biphenyls; BBD, benign breast disease; DDE, bis(4-chlorophenyl)-1,1-dichloroethene; DDT, bis(4-chlorophenyl)-1,1,1-trichloroethane; ER, estrogen receptor; PR, progesterone receptor; OC, organochlorine.

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zlsouer *et al*., 1999). Such chemical contaminants are known animal and/or human carcinogens. DDT and related organochlorine (OC) compounds are weakly estrogenic and can act as tumor promoters and inducers of cytochrome P450 enzymes. They are widely dispersed in the environment, and both DDE, the major persistent, environmental metabolite of DDT, and PCBs are almost universally present in the tissue of United States adults (Murphy *et al*., 1985; Lordo *et al*., 1996). Studies of the relationship of OC exposures to breast cancer risk have been reported in the past decade; most have found little or no association of measured residues in blood or adipose tissue with breast cancer (Krieger *et al*., 1994; Hunter *et al*., 1997; Zheng *et al*., 1999). However, some studies do find increased risks (Wolff *et al*., 1993; Hoyer *et al*., 1998; Aronson *et al*., 2000), and this has sustained interest in the hypothesis.

There is a notable lack of data on environmental exposures among Hispanic and African-American women, and even less information is available on cancer risk with respect to these differences. Higher levels of DDT in blood serum or adipose tissue have been found in African-Americans compared with Caucasians since the 1960s (Krieger *et al*., 1994; Zheng *et al*., 1999), but such exposures have been little investigated with respect to cancer risk. To address this question, we undertook a study of breast cancer in a metropolitan New York City hospital to examine potential environmental and genetic risk factors.

MATERIALS AND METHODS

Criteria for eligibility. The study population has been described previously (Weston *et al*., 1997). The sample included incident breast cancer patients, benign breast disease (BBD) control patients, and a second noncancer, non-BBD control group. Women with prior cancer (except nonmelanoma skin cancer), prior carcinoma *in situ* of the breast, or any history of benign breast disease with hyperplasia or atypia (current or prior) were ineligible. BBD control patients included women who were having surgical biopsies and women being screened for BBD. Women who underwent biopsies had pathologies that were mainly fibroadenoma, fibrocystic changes, and nonspecific benign pathology. The second control group was recruited from patients undergoing routine screening or minor surgical procedures in the same offices. Women were excluded from the second control group if they had prior cancer or breast disease (any chart notations or self-reports within the past 5 years). In total, 1101 women agreed to participate, a response rate of 65% that was comparable regardless of diagnosis or racial/ethnic designation. The resulting 175 case patients were frequency-matched by race within 5-year age groups to 181 BBD controls and 175 women in the second control group, using random numbers to select controls when their numbers exceeded the number of cases within a 5-year age group.

A questionnaire was administered by trained interviewers in person or by telephone to obtain baseline characteristics and reproductive history. Ethnic status was based on a woman's self-description. Smoking (ever) was defined as having smoked 100 or more cigarettes during one's lifetime. Alcohol intake (ever) was defined as having had 12 drinks of any kind of alcoholic beverage in any 1 year. Women were considered to be postmenopausal if their last menstrual period was at least 1 year prior to collection of blood, if they had undergone a bilateral oophorectomy, or if they had undergone a hysterectomy without a bilateral oophorectomy and were older than 54. If menstrual history information was unavailable, women were considered to be postmenopausal if they were more than 54 years old (Willett *et al.,* 1983). Family history of breast cancer was defined as any reported relative with breast cancer (parent, sibling, aunt/uncle, grandparent). A blood specimen was collected for analysis of serum OCs and lipids. Most specimens were obtained prior to surgery, and none were taken longer than 2 months after surgery, a protocol developed after two studies found that this interval does not affect OC levels (Gammon *et al*., 1996, 1997).

Laboratory methods. The method for determination of DDE and PCBs, including the quality control protocols, has been described previously (Wolff *et al*., 1993; Hunter *et al*., 1997). Limits of detection were less than 0.3 ng/mL for DDE and less than 1 ng/mL for HPCBs based on three times the standard deviation of the levels found in the lowest quality control serum pools (average concentration 0.3 ng/mL DDE, 0.9 ng/mL HPCB; $n = 43$ in 22 batches), following the International Union of Pure and Applied Chemistry definition (Long and Winefordner, 1983).

These or one of two higher level pools fortified with OCs were analyzed in duplicate in each analysis set (52 batches). In the mid-level pool, the CV for DDE was 20% (average 9 ng/mL), for HPCB 34% (4 ng/mL; $n = 40$); in the high pool, the CV for DDE was 13% (20 ng/mL), for HPCB 18% (9 ng/mL; $n = 19$). HPCBs reported here are the sum of the congener numbers 118, 153, 141, 138, 183, 187, 167, 174, 177, 156, 180, 170, 201, and 203. LPCBs are the

sum of congeners 28, 66, 74, 99, and 101. *trans*-Nonachlor and *p,p′*-DDT were also quantified. Serum cholesterol and triglycerides, determined by a commercial laboratory, were used to adjust serum organochlorine values to total serum lipids using the method of Akins *et al*., (1989).

Histologic analysis and immunohistochemical interpretation of tumors were performed by a breast pathologist (I.J.B.). Pathologic stage and tumor grade were derived utilizing standard grading techniques (modified Scarff–Bloom–Richardson grading scale; Elston *et al*., 1991). Estrogen receptor (ER) protein and progesterone receptor (PR) protein were assessed either by enzyme immunoassay (Abbott Labs, Abbott Park, IL), immunocytochemical analysis on frozen sections (Abbott Labs), or immunohistochemical studies on paraffin sections (ER-mAB clone 1D5 and PR-mAb clone PR2c5; Zymed, South San Franscisco, CA). P53 and Her-2/neu (erbB-2) protein expression were assessed by direct immunohistochemistry on paraffin sections using monoclonal antibodies AB-2 (clone PA 1801; Oncogene Science, Cambridge, MA) and CB- 11 (BioGenex, San Ramon, CA), respectively.

Statistics. For parametric analyses, DDE and PCB values were converted to logarithms to minimize the influence of a few very large observations and to better approximate normality. The effects of disease status and race on OC levels were made using ANOVA for two-way comparisons (cases vs two merged control groups and the three racial subgroups). The same analysis was used for continuous baseline characteristics. For dichotomous baseline characteristics (e.g., family history), a multiple logistic regression was used with the disease status (case vs pooled controls) and race as explanatory variable. Within-race comparisons were performed using one-way ANOVA or *t*-test for continuous measurements with no additional explanatory variables, χ^2 with $c-1$ degrees of freedom for unordered frequency data taking on c values, and χ^2 for trend with one degree of freedom (Mantel, 1963) for ordered categorical data. Tertiles of organochlorine exposure were constructed based on the frequency distribution of the controls, and relative risks for each tertile, together with confidence intervals, were as estimated by the odds ratios (ORs), as determined using unconditional multiple logistic regression. A test for trend was also performed by replacing tertiles with the logarithm of continuous variable (lipid-adjusted OC level) in the models. In the final models, adjustment was made for age, age-squared, menopausal status, and race. Other potential confounders considered were body mass index (BMI; kg/m^2), age at menarche, age at first full-term pregnancy, parity, any family history of breast cancer, months of lactation, tobacco use, alcohol intake, and hormone use. Analyses were performed using SAS-PC, Cary, North Carolina. All reported *P* values are two-sided. *P* values <0.05 are considered statistically significant, *P* values <0.10 are reported, and those >0.10 are indicated as not significant (NS).

RESULTS

Our study group included African-American ($n=41$), Hispanic ($n=32$), and Caucasian ($n=102$) case patients who were diagnosed with breast cancer in New York City. Controls included approximately equal numbers of BBD ($n=181$) and patients in the second control group ($n=175$), matched by racial/ethnic status and frequency-matched on age. Baseline characteristics (Table 1) showed cases and controls to have similar ages at diagnosis for women undergoing biopsies (cancer or BBD) or at recruitment date (controls). Age at menarche as well as histories of breastfeeding were comparable. Approximately 40% were premenopausal. The BBD patients were comparable to the second control group with respect to all variables of interest, and therefore they were combined for the purposes of case-control comparisons.

A number of risk factors varied among racial/ethnic groups (Table 2). African-American cases were slightly but not significantly older than their controls. Age at first birth was younger among African-American and Hispanic women than among Caucasian women (Table 2). In addition, fewer Caucasian than Hispanic women had more than one full-term pregnancy. Age at menopause tended to be later among Caucasian than African-American or Hispanic women. Average BMI (kg/m^2) was higher and years of education were lower among African-American and Hispanic women, whereas more Caucasian women were currently employed outside the home. Fewer Hispanics had ever consumed alcohol or smoked cigarettes than African-Americans or Caucasians. A higher proportion of Caucasian women reported any family history of breast cancer; the lowest reported frequency of a family history was among Hispanic control women (4/62; 6%).

Significant differences between cases and controls were observed only for age at first birth (Table 2). Other variables, including parity, family history, BMI, smoking history, alcohol history, and reproductive factors, were not significantly different with

TABLE 1
Baseline Characteristics of Cases and Controls for Characteristics That Did Not Differ by Race

	Cases		BBD controls		Second control group	
Age (mean ± SD, *N*)	56 ± 13	(175)	54 ± 12	(181)	55 ± 12	(175)
African-American	41	(23%)	40	(22%)	36	(21%)
Hispanic	32	(18%)	40	(22%)	39	(22%)
Caucasian	102	(58%)	101	(56%)	100	(57%)
Age at menarche	12.7 ± 1.93	(163)	12.6 ± 1.55	(165)	12.6 ± 1.70	(164)
Ever breast feeding[a] (*N*, %)	47/109	(43%)	47/118	(40%)	54/124	(44%)
Lifetime lactation, months						
Parous women (*N*)	5.6 ± 11	(109)	5.1 ± 13	(118)	5.1 ± 10	(124)
Ever lactated only[b]	13 ± 15	(47)	13 ± 19	(47)	12 ± 13	(54)
Number premenopausal	60/163	(37%)	72/166	(44%)	64/164	(39%)
Oral contraceptives used	68/151	(45%)	75/164	(46%)	78/164	(48%)

Note. Not all variables were available on all subjects. There were no significant differences between cases and controls. BBD (benign breast disease) controls and the second control group also did not differ ($P > 0.1$).
[a]Among parous women.
[b]Among parous women who lactated, a subset of parous women.

respect to case-control status, adjusting for race. Tumor stage, based on size and node positivity, was less advanced among Caucasian women, who had more stage 1 or DCIS (69%) than African-Americans (45%) and Hispanics (48%) in this group of women (Table 3).

TABLE 2
Baseline Characteristics of Cases and Controls for Characteristics That Differed by Race

	African-American				Hispanic				Caucasian			
	Cases		Both control groups		Cases		Both control groups		Cases		Both control groups	
Age, years	59.2 ± 13.2	(41)	55.5 ± 12.2	(76)	52.7 ± 13.6	(32)	53.6 ± 12.9	(79)	56.4 ± 12.7	(102)	54.9 ± 10.9	(201)
United States born[a] (*N*, %)	30/35	(86%)	63/70	(90%)	16/23	(70%)	43/60	(72%)	80/90	(89%)	164/191	(86%)
Age at first full-term pregnancy[b] (mean ± SD, *N*)	21.3 + 6.12	(29)	21.5 ± 5.26	(57)	24.2 ± 7.70	(26)	21.6 ± 5.20	(54)	27.8 ± 6.15	(60)	25.4 ± 5.08	(131)
No. of full-term pregnancies[c]												
0	8/37	(22%)	15/72	(21%)	3/29	(10%)	10/65	(18%)	34/93	(35%)	62/194	(32%)
1	8/37	(22%)	16/72	(22%)	8/29	(28%)	11/65	(17%)	20/93	(21%)	18/194	(9.3%)
>1	21/37	(57%)	41/72	(57%)	18/29	(62%)	44/65	(68%)	43/93	(44%)	114/194	(58%)
Employed[b] (*N*, %)	12/35	(34%)	24/78	(34%)	2/25	(8%)	18/64	(28%)	58/90	(64%)	99/192	(52%)
Education, years[b] (mean ± SD, *N*)	12.2 ± 2.46	(36)	12.7 ± 3.48	(72)	11.7 ± 3.98	(25)	11.2 ± 4.37	(64)	15.3 ± 3.03	(97)	15.6 ± 2.55	(193)
Age at menopause[b]	47 ± 6.8	(28)	44 ± 7.5	(44)	47 ± 6.5	(13)	46 ± 7.7	(33)	49 ± 5.6	(55)	48 ± 6.3	(115)
Any family history of breast cancer[d]	6/37	(16%)	19/72	(26%)	6/29	(21%)	4/62	(6%)	39/96	(41%)	78/117	(40%)
Postmenopausal hormone use[c]	4/36	(11%)	12/71	(17%)	3/25	(12%)	6/64	(9.4%)	13/91	(14%)	46/193	(24%)
BMI (kg/m^2)[b] (mean ± SD, *N*)	28.4 ± 5.29	(37)	30.1 ± 6.73	(72)	28.4 ± 5.89	(29)	28.6 ± 6.10	(64)	24.8 ± 5.06	(97)	24.3 ± 4.96	(193)
Ever drank[d] (*N*, %)	18/36	(50%)	32/71	(45%)	7/25	(18%)	11/64	(17%)	63/91	(69%)	137/193	(71%)
Ever smoked[a] (*N*, %)	21/36	(59%)	39/70	(56%)	14/25	(61%)	17/64	(27%)	51/91	(58%)	95/192	(55%)

Note. Cases and controls did not differ except for age at first pregnancy, $P = 0.021$. Continuous variables were analyzed using ANOVA (case status and race); discrete variables were analyzed using logistic regression with race and case status as predictors.
[a]Afr. A./Cau. > Hisp.
[b]Cau. ⟨⟩Afr. A./Hisp.
[c]Cau. ⟨⟩Hisp.
[d]Cau. > Afr. A. > Hisp.

TABLE 3

Tumor Stages among Cancer Cases by Racial/Ethnic Status among Breast Cancer Patients in New York City (1997)

	N	DCIS	Stage 1	Stage 2	Stage 3
African-American	38	4(11%)	13(34%)	16(42%)	5(13%)
Hispanic	29	1(3.5%)	13(45%)	13(45%)	2(6.9%)
Caucasian	100	18(18%)	51(51%)	30(30%)	1(1.0%)
Total	167	23(14%)	77(46%)	59(35%)	8(4.8%)

Note. χ^2 for ordered outcomes to test the trend of stage across racial/ethnic groups (Mantel–Haenzsel); $P < 0.001$.

TABLE 4

Positivity of Tumor Markers among Cancer Cases by Race

	Tumor markers positive (*N*/total, %)			
	ER$^+$	PR$^+$	erbB-2$^+$	p53$^+$
African-Americans	25/35(71%)	18/35(51%)	17/40(43%)	15/40(38%)
Hispanics	18/29(62%)	16/29(55%)	12/32(38%)	10/32(31%)
Caucasians	69/90(77%)	61/90(68%)	34/100(34%)	22/101(22%)
Total	112/154(73%)	95/154(62%)	63/172(37%)	47/173(27%)

Note. None of the racial/ethnic differences were significant (χ^2 test).

We measured four tumor markers among case patients (Table 4). Positivity of ER, PR, p53, and erbB-2 (Her-2/neu) showed no significant differences among the three racial/ethnic groups. ER positivity decreased with increasing tumor stage (86, 79, 60% for stage 0, 1, 2 or higher; $n = 147$; P(Mantel–Haenzsel) = 0.007). The trend for PR was similar but not statistically significant, whereas p53 expression also increased with stage (13, 21, 39% for stages 0, 1, ≥ 2; $n = 165$; P(Mantel–Haenzsel) = 0.004). erbB-2 expression increased with stage but the trend was not significant (26, 36, 40% for stages 0, 1, ≥ 2; $n = 165$; P(Mantel–Haenzsel) > 0.4).

We measured three organochlorine pesticide residues (*p,p′*-DDE; *p,p′*-DDT; *trans*-nonachlor) as well as PCBs. DDE was higher than HPCBs on average among African-American and Hispanic women but not among Caucasians. DDT and *trans*-nonachlor were low, on average less than 0.05 μg/g (geometric mean of lipid-adjusted levels). After adjusting for lipids, we observed significantly higher levels of DDE among African-American than Hispanic and than Caucasian women and higher HPCB and *trans*-nonachlor levels among African-American women (Table 5). DDT was highest and LPCB was lowest among Hispanic women. We found no consistent

TABLE 5

DDE, PCB, and *trans*-Nonachlor Levels by Race and Diagnosis

Serum levels (ng/mL)	All						African-American						Hispanic						Caucasian					
	Cases			Controls			Cases			Controls			Cases			Controls			Cases			Controls		
	GM	(GSD)	*N*	GM	(GSD)	*N*	GM	(GSD)	*N*	GM	(GSD)	*N*	GM	(GSD)	*N*	GM	(GSD)	*N*	GM	(GSD)	*N*	GM	(GSD)	*N*
p,p′-DDE[a]	4.1	(3.06)	164	4.3	(2.82)	341	7.2	(2.62)	35	6.4	(2.75)	69	4.6	(2.94)	30	5.0	(3.32)	78	3.2	(3.03)	99	3.9	(2.53)	194
p,p′-DDT[b]	0.20	(2.11)	163	0.19	(2.14)	335	0.22	(2.01)	35	0.17	(1.87)	68	0.26	(2.56)	30	0.23	(2.72)	77	0.17	(1.97)	98	0.18	(1.96)	190
HPCB[c]	4.0	(1.91)	152	4.1	(1.89)	325	5.5	(1.71)	35	5.4	(1.92)	65	2.6	(1.85)	26	3.0	(1.89)	76	4.0	(1.87)	91	4.2	(1.79)	185
LPCB[d]	0.75	(1.91)	136	0.75	(1.92)	275	0.84	(2.21)	33	0.72	(2.14)	61	0.47	(1.70)	26	0.60	(1.81)	69	0.85	(1.83)	77	0.84	(1.83)	145
trans-Nonachlor[c]	0.23	(2.25)	161	0.24	(2.31)	333	0.31	(2.31)	35	0.28	(2.26)	67	0.18	(2.54)	29	0.19	(2.49)	75	0.22	(2.09)	97	0.24	(2.23)	191
Adjusted for lipids, μg/g																								
p,p′-DDE[a]	0.61	(3.02)	161	0.66	(2.73)	339	1.1	(2.67)	33	1.0	(2.72)	69	0.71	(3.04)	30	0.75	(3.19)	78	0.48	(2.93)	98	0.55	(2.45)	193
p,p′-DDT[e]	0.030	(2.14)	160	0.028	(2.09)	333	0.034	(1.92)	33	0.026	(1.79)	68	0.039	(2.71)	30	0.035	(2.69)	77	0.026	(1.99)	97	0.027	(1.91)	188
HPCB[c]	0.60	(1.88)	149	0.62	(1.86)	323	0.81	(1.72)	33	0.80	(1.88)	64	0.40	(1.87)	26	0.44	(1.88)	76	0.060	(1.83)	90	0.65	(1.74)	183
LPCB[d]	0.11	(2.00)	133	0.11	(1.89)	273	0.13	(2.37)	31	0.11	(2.14)	61	0.072	(1.91)	26	0.089	(1.83)	69	0.13	(1.77)	76	0.13	(1.76)	143
trans-Nonachlor[c]	0.035	(2.22)	158	0.036	(2.19)	331	0.046	(2.37)	33	0.042	(2.19)	67	0.028	(2.62)	29	0.028	(2.33)	75	0.033	(2.01)	96	0.038	(2.10)	189
Serum lipids, g/L mean ± SD	6.74 ± 1.47		164	6.69 ± 1.33		343	6.77 ± 1.37		34	6.75 ± 1.15		69	6.76 ± 1.71		31	6.76 ± 1.22		78	6.73 ± 1.44		99	6.64 ± 1.44		196

Note. GM (geometric mean) and geometric standard deviation (GSD) are presented for the OCs. The log-transformed values were analyzed using ANOVA (case status and race). There were no case-control differences.

[a] Afr. A. > Hisp. > Cau.

[b] Hisp. > Cau.

[c] Afr. A. > Cau. > Hisp.

[d] Afr. A./Cau. > Hisp.

[e] Hisp. > Afr. A./Cau.

TABLE 6
Risk of Breast Cancer Associated with DDE and HPCB Levels

	Concentration of DDE within tertiles (lipid-adjusted μg/g)			
	0–0.44	0.45–1.03	> 1.04–12.9	Total
OR(CI)	1.0	0.80(0.49–1.3)	0.93(0.56–1.5)	P(trend) = 0.499
N, cases	56	42	53	151
N, controls	106	104	107	317
	Concentration of DDT within tertiles (lipid-adjusted μg/g)			
	0–0.0207	0.0208–0.033	0.034–1.3	Total
OR(CI)	1.0	1.19(0.73–2.0)	1.34(0.82–2.2)	P(trend) = 0.241
N, cases	44	50	56	150
N, controls	108	105	101	314
	Concentration of DDT within tertiles (ng/mL, not lipid-adjusted)			
	0–0.12	0.13–0.23	> 0.23–9.62	Total
OR(CI)	1.0	1.7(1.06–2.9)	1.7(1.004–3.0)	P(trend) = 0.233
N, cases	34	63	55	152
N, controls	106	110	99	315
	Concentration of HPCB within tertiles (lipid-adjusted μg/g)			
	0.079–0.459	0.460–0.798	0.799–3.3	Total
OR(CI)	1.0	0.88(0.52–1.5)	0.78(0.45–1.3)	P(trend) = 0.220
N, cases	48	46	46	140
N, controls	94	102	104	300
	Concentration of LPCB within tertiles (lipid-adjusted μg/g)			
	0–0.084	0.085–0.162	0.163–2.39	Total
OR(CI)	1.0	1.47(0.84–2.6)	0.96(0.53–1.7)	P(trend) = 0.758
N, cases	32	54	38	124
N, controls	78	86	88	252
	Concentration of *trans*-nonachlor within tertiles (lipid-adjusted μg/g)			
	0–0.025	0.026–0.049	0.050–0.693	Total
OR(CI)	1.0	0.99(0.61–1.6)	0.73(0.43–1.2)	P(trend) = 0.354
N, cases	51	54	44	149
N, controls	100	105	107	312

Note. Tertiles were determined among controls. ORs (odd ratios) and CI (95% confidence limits) were derived from logistic regression models adjusted for age, age^2, menopausal status, and race. Other predictors, including BMI, family history, lactation history, and parity, were not significant.

associations between OC levels and breast cancer risk (Tables 5 and 6). *p,p′*-DDT was slightly higher among African-American cases than controls (Table 5), and there was a suggestive increasing risk with tertiles of DDT among all women (Table 6). However, the trends were not significant. Of methodologic interest was the effect of lipid adjustment for DDT. For DDT (unadjusted), the odds ratios for the mid and high tertiles were significantly elevated (OR 1.7, CI 1.004–3.0 in the highest tertile) and remained significant if serum lipids were included in the model, although the trend for DDT as a continuous variable was not significant. Using tertiles of DDT for which the serum levels were individually adjusted for serum lipids, none of these same associations were statistically significant.

We also analyzed the risk of breast cancer with respect to OC exposure stratified by race, BMI, age, parity/lactation, and menopausal status (data not shown). There were no significant findings overall, but the confidence intervals were wide, with small numbers in certain strata. We examined levels of organochlorines in relation to tumor markers (Table 7). DDE, DDT, and HPCBs were higher in women

TABLE 7
Levels of DDE and PCBs by Tumor Markers (Geometric Mean(GSD, *N*))

Serum levels (μg/g lipid)	All		Adjusted GM	
	ER$^-$	ER$^+$	ER$^-$	ER$^+$
p,p′-DDE	0.52(2.53, 35)	0.65(3.31, 106)	0.70	0.79
p,p′-DDT	0.026(2.16, 35)	0.033(2.20, 105)	0.028	0.037
HPCB	0.47(1.75, 33)	0.66(1.94, 99)	0.53	0.63
	p53 +	p53 −	p53 +	p53 +
p,p′-DDE	0.60(3.10, 120)	0.62(2.82, 40)	0.73	0.82
p,p′-DDT	0.031(2.15, 120)	0.026(2.10, 39)	0.035	0.030
HPCB	0.61(1.90, 108)	0.55(1.83, 40)	0.60	0.58
	erbB-2$^-$	erbB-2$^+$	erbB-2$^-$	erbB-2$^+$
p,p′-DDE	0.62(3.09, 102)	0.62(2.78, 57)	0.74	0.80
p,p′-DDT	0.031(2.23, 101)	0.029(2.00, 57)	0.033	0.035
HPCB	0.61(1.86, 90)	0.58(1.91, 57)	0.59	0.60

Note. *P* values for ANOVA (+ vs − marker) were > 0.05. ANOVA and the GM were adjusted for age, race, and menopausal status; none of the adjusted GMs were significantly different with respect to tumor marker.

with ER-positive tumors than in those with ER-negative tumors, but the differences were not significant after adjusting for age, BMI, menopausal status, and race.

To examine potential determinants of OC exposure, we compared several risk factors in relation to tertiles of DDE and PCBs among 342 control patients (lipid-adjusted values; Tables 8–10). OC levels (lipid-adjusted DDE, HCPB, LPCB, *trans*-nonachlor) increased with age ($r_S = 0.15$–0.36; $P < 0.01$; $n = 340$) and were intercorrelated ($r_S = 0.24$–0.68; $P < 0.01$), an effect that was not attenuated by adjusting for age (Table 10). Some associations differed for DDE and PCBs. DDE levels were positively correlated with BMI, and DDE showed an inverse correlation with education level (years) DDE was lower among nulliparous women and women reporting a family history of breast cancer, controlling for age and race. In contrast, HPCB levels decreased with BMI but were not correlated with parity, lactation, or family history of breast cancer. The distribution of these risk factors across DDE and HPCB tertiles was similar for tertiles of all control women or for race-specific tertiles of organochlorines. Proportions of women in the three racial/ethnic groups showed the trends expected from the differences that were seen in OC levels overall; i.e., there were more African-Americans and Caucasians in the higher tertiles of DDE and HPCBs. Neither DDT, *trans*-nonachlor, nor LPCB were associated with BMI, but *trans*-nonachlor, LPCB, and HPCB were more strongly correlated with each other than with DDE or DDT (adjusted for age; Table 10).

TABLE 8
Exposures and Other Risk Factors for Breast Cancer by Tertile of DDE among Control Women

	Tertiles of DDE serum concentration (lipid adjusted)			
	Low ($n = 113$)	Mid ($n = 113$)	High ($n = 113$)	P^a
Median serum levels (μg/g lipid)				
DDE	0.26	0.69	1.6	
DDT	0.022	0.024	0.035	< 0.01
HPCB	0.43	0.62	0.86	< 0.01
LPCB	0.094	0.11	0.16	< 0.01
trans-nonachlor	0.026	0.034	0.050	< 0.01
Age, years	49	53	59	< 0.01
African-American $n = 69$	14	16	39	< 0.01
Hispanic $n = 78$	25	25	28	NS
Caucasian $n = 193$	74	72	47	0.02
Age at menarche, years	12	13	13	NS
Nulliparity	35/106(33%)	28/104(27%)	23/108(21%)	0.054
Never lactated, parous	41/71(58%)	42/76(55%)	51/83(61%)	NS
Family history of breast cancer	39/106(37%)	28/105(27%)	27/108(25%)	0.059
BMI (kg/m^2)	23.3	23.8	26.9	< 0.01
Total serum lipids (g/L)	6.3	6.5	6.5	NS

Note. Median values are given for continuous variables.
[a] *P* for r_S or for trend (Mantel–Haenszel).

TABLE 9
Exposures and Other Risk Factors for Breast Cancer by Tertile of HPCBs among Control Women

	Tertiles of HPCB serum concentration (lipid adjusted)			
	Low ($n = 107$)	Mid ($n = 108$)	High ($n = 108$)	P^a
Median serum levels (μg/g lipid)				
HPCBs	0.34	0.61	1.2	
DDE	0.40	0.66	1.1	< 0.01
DDT[a]	0.022	0.025	0.033	< 0.01
LPCB	0.066	0.11	0.20	< 0.01
trans-Nonachlor	0.022	0.036	0.064	< 0.01
Age, years	49	56	58	< 0.01
African-American	14/64	15	35	< 0.01
Hispanic	45/76	18	13	< 0.01
Caucasian	48/183	75	60	0.06
Age at menarche, years	12	12	13	NS
Education, years	14	16	14	NS
Nulliparity	25/95(26%)	27/102(26%)	27/104(26%)	NS
Never lactated, parous	35/69(51%)	45/74(61%)	47/77(61%)	NS
Family history of breast cancer	25/95(26%)	34/103(33%)	32/104(31%)	NS
BMI (kg/m^2)	26.6	23.8	24.1	NS
Total serum lipids (g/L)	6.6	6.4	6.5	NS

Note. Median values are given for continuous variables.
[a]P for r_S or for trend (Mantel–Haenszel).
[b]Means of DDT (as ng/mL) across tertiles were 0.055, 0.037, 0.046.

DISCUSSION

In this hospital-based case-control study we investigated risk for breast cancer associated with organochlorine exposure among 175 cancer patients, 181 control patients with BBD, and 175 women in a second hospital control group. Minority women had slightly higher-stage tumors, yet their tumor markers (ER, PR, p53, erbB-2) were not significantly different among African-American, Hispanic, and Caucasian women. These similarities have been observed in larger series of patients (Elledge *et al*., 1994).

TABLE 10
Age-Adjusted Spearman Correlation Coefficients for OC Levels and Body Mass Index in Controls among 337 New York City Women

Lipid-adjusted OCS	DDT	*trans*-Nonachlor	HPCB	LPCB	Body mass index
DDE	0.33[a]	0.21[a]	0.34[a]	0.25[a]	0.22[a]
DDT		0.16[b]	0.25[a]	0.21[a]	− 0.02
TN			0.56[a]	0.59[a]	0.010
HPCB				0.66[a]	− 0.15[b]
LPCB					− 0.07

[a]$P < 0.01$
[b]$P < 0.05$, Not all correlations had all observations.

OC levels were significantly higher among minority than Caucasian women. Higher residues of DDT have been observed previously among African-Americans (Krieger *et al*., 1994; Schidkraut *et al*., 1999; Zheng *et al*., 1999), but few data exist on OC levels among Hispanics. Our data suggest that minorities have higher levels of some but not all OCs than Caucasians. However, these exposures were not associated with increased breast cancer risk in our study, regardless of ethnicity. This finding is consistent with numerous recent reports that have observed no significant elevations in risk associated with organochlorines (Hunter *et al*., 1997; Helzlsouer *et al*., 1998; van't Veer *et al*., 1997). Nonetheless, not all studies have been negative (Hoyer *et al*., 1998; Aronson *et al*., 2000; Wolff *et al*., 1993), and some groups have found higher risk in certain subgroups of women (Dorgan *et al*., 1999; Moysich *et al*., 1998). In addition, there have been preliminary reports of associations between OC exposures and tumor aggressivity (Dewailly *et al*., 1999). African-American women, who have higher OC levels, have poorer survival than Caucasian women, even among postmenopausal women (Chu *et al*., 1999); neither medical care access nor socioeconomic status explains this pattern (Yood *et al*., 1999; Lannin *et al*., 1998). The question of whether environmental

factors may play a role in these differences has not been addressed. Thus, there are opportunities for further research that will require large populations to detect possible risks in stratified samples.

Presumably, OC levels and their variability among ethnic groups are attributable to several factors, such as diet, including fish consumption, and other environmental sources, including rural residence (Laden *et al*., 1999; Kostyniak *et al*., 1999; Schildkraut *et al*., 1999). Although we do not have specific information to establish origins of exposure, we found strong correlations among different OCs, as well as between OCs and age, consistent with common routes of exposure to OCs. The stronger correlation of *trans*-nonachlor with PCB than with DDT residues suggests that *trans*-nonachlor exposures may arise from the same environmental sources of chlordane contamination (e.g., fish) and/or during the same time period. The trends of PCB and *trans*-nonachlor levels were also different from the trends for DDE and DDT; i.e., African-Americans had the highest and Hispanics had the lowest levels each of HPCB, LPCB, and *trans*-nonachlor, whereas Caucasians had the lowest levels of DDT. Chlordane residues including a large proportion of *trans*-nonachlor are prominent contaminants of fish in the waterways around New York City. PCB levels are the highest specific OC component in fish (in the range of 1 ppm wet weight on average), whereas DDT residues are about 0.1–0.2 ppm and chlordane components are somewhat less (*ca*. 0.05 ppm; New York State, 1996). These proportions vary in different species and different parts of the harbor, but the relative trends are consistent (*i.e.,* PCBs $\gg$ DDTs $>$ chlordanes). *trans*-Nonachlor may also be derived directly from chlordane as a result of indoor exposures following its use as a termiticide. The levels of DDE relative to those of PCBs are also of interest; whereas DDE has in the past been the highest environmental OC residue found in humans, this has changed; average DDE levels were higher than PCBs in African-American and Hispanic women, but not in Caucasian women in our study.

The magnitude and the direction (inverse or positive) of relationships between BMI, age, and OC levels reflect accumulation and turnover rates, as well as changes over time in exposures (i.e., increased or decreased environmental contamination and absorption). The positive association between OCs and age indicates their longterm absorption and slow metabolism. The positive association of DDE levels with BMI suggests that turnover may be slower among obese women, as we have discussed previously (Wolff and Anderson, 1999a,b). In our study, minority women had higher BMI on average; therefore, this may have contributed to their higher *current* levels of certain OC compounds. Innate metabolism may also differ among racial/ethnic groups, which can affect long-term disposition of OCs, as well as breast cancer risk (Flaws and Bush, 1998; Wolff and Weston, 1997). The negative association between HPCBs and BMI, as we have proposed in earlier research (Wolff and Anderson, 1999a), suggests ongoing exposure to this environmental contaminant at a pace that competes with its elimination rate. The higher mean level of PCBs relative to DDE in Caucasian women in our study further supports this view.

Associations between OC levels and reproductive factors represent nonmetabolic fluctuations in the body burden of persistent compounds. For example, the inverse association of DDE with family history of breast cancer among controls may arise from a higher number of young women with such a history seeking screening in the hospital setting; we observed such a pattern in another study (Wolff *et al*., 2000). Similarly, this pattern may explain the higher prevalence of nulliparous women with low DDE levels. HPCB levels were not associated with these reproductive factors. We did not find significant negative correlations between OC levels and lactation history or parity, in contrast to what might be expected, in that it has been well documented that lactation lowers the body burden of OCs (half-lives of several months; Gladen and Rogan, 1995).

In summary, we find no association between OC levels and breast cancer risk in our study. Overall, African-American women had highest levels of DDE, HPCB, and *trans*-nonachlor, whereas Hispanic women had higher levels of DDE and DDT but not HPCB than Caucasian women, and HPCB, LPCB, and *trans*-nonachlor were lowest among Hispanic women.

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